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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,874	11/03/2003	Arthur Kunz	AM100788 P1	4900

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/699,874	KUNZ ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-144* is/are pending in the application.

4a) Of the above claim(s) *1-112 and 136-141* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *113-135 and 142-144* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The Election filed on May 22, 2006 in response to the Restriction Requirement of February 23, 2006 has been entered. Applicant's election of Group XIV, claims 113-135 and 142-144, as specifically drawn to a method of treating a subject with a proliferative disorder, comprising administering a therapeutically effective dose of a composition comprising a monomeric cytotoxic drug derivative/carrier conjugate with one or more bioactive agents, wherein the bioactive agent is an antibody without traverse has been acknowledged.

The restriction requirement is therefore deemed to be proper and is made FINAL.

Claims 1-144 are currently pending.

Claims 1-112 and 136-141 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 113-135 and 142-144 are currently under consideration.

Species Election

Applicant's election of calicheamicins as the species of cytotoxic drug, Claim 128, and CHOP as the species of cytotoxic drug combination are acknowledged. However, the Examiner has withdrawn the species election upon reconsideration.

Information Disclosure Statement

The Information Disclosure Statement filed on 5/27/2004 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

Specification

The disclosure is objected to because of the following informalities:

The specification is objected to for improper disclosure of amino acid sequences and/or nucleotide sequences without a respective sequence identifier, i.e. a SEQ ID NOs:, see for example Figures 2, 3, 4 ect.. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821

through 1.825. In the absence of a sequence identifier for each sequence, Applicant must provide a computer readable form (CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d).

Appropriate correction is required.

Claim Objections

Claims 113 and 131 are objected to because of the following informalities:

Claim 113 is drawn to a method of treating a subject with a proliferative disorder comprising administering a therapeutically effective dose of the composition of claim 91. However, claim 91 is drawn to a non-elected invention. Applicant's can overcome this objection by incorporating the composition of claim 91 into claim 113. For examination purposes, the composition will be interpreted as comprising a therapeutically effective dose of a monomeric cytotoxic drug derivative/carrier conjugate.

Claim 131 recites a series of bioactive agents such as growth factors, hormones, cytokines and anti-hormones which are non-elected inventions.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 144 is rejected as vague and indefinite for reciting the term CMC-544 as the sole means of identifying the claimed molecule. The use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. Amending the claims to specifically and uniquely identify CMC-544, for example, by structure can obviate the rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 113-123 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are inclusive of a cytotoxic drug derivative/carrier conjugate. Therefore, the claims encompass a genus of molecules defined solely by its principal biological property, which is simply a wish to know the identity of any material with that biological property. However, the written description in this case only sets forth one species of cytotoxic drug derivative/carrier conjugates, wherein the carrier conjugate is an anti-CD22 antibody.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164).

The specification teaches (page 5, lines 21-24) that the carriers of the conjugates of the present invention include, but are not limited to, hormones, growth factors, antibodies, antibody fragments, antibody mimics, and their genetically or enzymatically engineered counterparts. The specification further teaches that the essential property of the carrier is its ability to recognize and bind to an antigen or receptor associated with undesired cells and to be subsequently internalized (page 21, lines 25-27). In addition, the specification teaches that the preferred carriers for use in the present invention are antibodies and antibody mimics. Specifically, the specification antibodies directed toward the CD22 cell surface antigen (page 23, lines 27+). Thus, while the specification reasonably conveys one species of carrier, e.g., anti-CD22 antibodies, there is insufficient written

description encompassing the genus of carriers because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics are not set forth in the specification as-filed. A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of carriers that encompass the genus nor does it provide a description of structural features that are common to the genus. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever*

is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus carriers, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an anti-CD22 antibody, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 113-123 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating cancer comprising administering a therapeutically effective amount of a composition comprising a cytotoxic drug derivative conjugated to an antibody which specifically binds to a tumor cell antigen, does not reasonably provide enablement for a method of treating any and/or all proliferative disorders comprising administering a therapeutically effective amount of a composition comprising a cytotoxic drug conjugated to any and/or all carriers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404).

Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims are drawn to a method of treating a proliferative disorder, comprising administering a therapeutically effective amount of a cytotoxic drug derivative conjugated to a carrier agent. The invention is in a class of invention which the CAFC has characterized as "the

unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of treating any and/or all-proliferative disorders comprising administering a therapeutically effective amount of a composition comprising a cytotoxic drug conjugated to any and/or all carriers. As such, the claims are not specifically directed to methods comprising administering a conjugate comprising an antibody that binds an antigen expressed by the cells affected by the disorder, but are instead more broadly directed to conjugates comprising any of a genus of structurally and/or functionally disparate "carriers", which do not necessarily bind or target those cells.

Guidance in the specification and Working Examples

The specification teaches the in vivo and in vitro effects of CMC-544 on CD22 B-cell lymphoma cell lines and tumors (beginning on page 57, Example 6). Specifically, the reference teaches that CD22-mediated delivery of calicheamicin to the CD22+ cells via the conjugate CMC-544 was at least 10 times more efficient in killing tumor cells that the unconjugated drug itself (page 57, lines 26-30, Tables 4 and 5). In contrast, the specification teaches that the control conjugate, CMA-676, showed cytotoxicity that was either les than or similar to the unconjugated calicheamicin derivate (page 57, lines 30-32). With regards to CMC-544 and CMA 676, the specification teaches that the CMC conjugate comprises calicheamicin conjugated to an anti-CD22 antibody and CMA-676 is calicheamicin conjugated to an anti-CD33 antibody (page 55, lines 20-30 and page 56, line 27 to page 57). Thus, while the claims encompass treating any and/or all proliferative disorders comprising administering a cytotoxic drug derivative conjugated to any and/or all carriers, the specification only reasonably conveys a method of treating cancer comprising administering a cytotoxic drug derivative conjugated to an antibody specific for a tumor cell antigen. In particular,

treatment of B-cell malignancies comprising administering a cytotoxic drug derivative conjugated to an antibody which binds CD22 antigens. While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of any proliferative disease including cancer, is required for practice of the claimed invention.

Quantity of experimentation

The quantity of experimentation in the areas of cancer therapy is extremely large given the unpredictability associated with treating cancer in general and the lack of correlation of in vitro findings to in vivo success, and the fact that no known cure or preventive regimen is currently available for cancer.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that there needs to be a direct correlation between the proliferative disorder being treated and the carrier, which is used as evidenced by the prior art cited below (US Patents: 5,134,075; 5,686,072; 6,183,477 and Ghetie et al.). Moreover, it is well known that the art of drug discovery for is highly unpredictable. With particular regard to anticancer drug discovery, Gura (*Science.* 1997; **278**: 1041-1042), for example, teaches that researchers are faced with the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Because of a lack of predictability, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, and indicates that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2). Gura very succinctly teaches our lack in ability to reliably extrapolate pre-clinical data to accurately predict the outcomes of such treatments in humans is due to the fact that "xenograft tumors don't behave like naturally occurring tumors in humans" (page 1041, column 2). Gura teaches that although researchers had hoped that xenografts would prove to better models for studying cancer in humans and screening candidate therapeutic agents for use in treating patient diagnosed with cancer, "the results of xenograft screening turned out to be not much better than

those obtained with the original models". Gura states that as a result of their efforts, " '[w]e had basically discovered compounds that were good mouse drugs rather than good human drugs' ".

Saijo et al. (*Cancer Sci.* 2004 Oct; **95** (10): 772-776) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Conclusion

Applicant is reminded, reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify conjugates of cytotoxic agents and carriers, which are therapeutically effective to treat a proliferative disorder; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification

disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 113-116 and 122-123 are rejected under 35 U.S.C. 102(b) as being anticipated by Hellstrom et al. (US 5,134,075, 1992).

Hellstrom et al. teach a novel monoclonal antibody which binds strongly to a protein associated with human tumors, including carcinomas, as well as sarcomas (abstract). Moreover, the patent teaches a method of treating human tumors comprising administering a therapeutically effective amount of an antibody in conjunction with an appropriate therapeutic agent, wherein the antibody can be conjugated or linked to a therapeutic agent for delivery of the therapeutic agent to the site of the cancer (abstract and column 8, lines 47-55). For example, the patent teaches that the antibody can be used as a carrier of various agents which have an antitumor effect, including, but not restricted to, chemotherapeutic drugs, toxins, immunological response modifiers and radioisotopes (column 3, lines 57-61). With regards to the administration, the patent teaches that the immunoconjugate can be administered using conventional modes of administration including, but not limited to, intravenous (column 9, lines 62-66).

Claims 113, 124-125, 127, 131-134 and 142 are rejected under 35 U.S.C. 102(b) as being anticipated by Ghetie et al. (Blood 1992; 80: 2315-2320) as evidenced by Newton et al. (Blood 2001; 97: page 528-535).

Ghetie et al. teach a method of treating a lymphoma, comprising administering a therapeutically effective amount of a cytotoxic drug/carrier conjugate referred to as RFB4-dgA,

wherein the cytotoxic drug is deglycosylated ricin A chain and the carrier is an antibody directed against the CD22 antigen (page 2317, , 1st column, 2nd to last sentence bridging 2nd column and Table 3). Moreover, the reference teaches a method of treating disseminated Daudi lymphoma comprising administering a therapeutically effective amount of the immunologic conjugate RFB4-dgA with an antibody directed against the CD19 antigen, wherein the combination of the anti-CD19 antibody and immunologic conjugate had significant antitumor activity (abstract and page 2318, Table 6). With regards to the administration, Ghetie et al. teach that the immunologic conjugate was administered retroorbitally (page 2316, 1st column, *IT therapy*). Thus, while Ghetie et al. do not explicitly teach that Daudi lymphoma is a B cell malignancy, the claimed limitation does not appear to result in a manipulative difference in the prior arts method because as evidenced by Newton et al. Daudi lymphoma are human B-cell tumors (page 531, 1st column, 2nd full paragraph). See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Claims 113-121, 124-127, 131-134 and 142 are rejected under 35 U.S.C. 102(b) as being anticipated by Uhr et al. (US 5,686,072, 1997).

Uhr et al. teach a method of treating a B cell malignancy in a patient comprising administering a therapeutically effective amount of a combination of an anti-CD19 antibody and anti-CD22 immunotoxin, wherein the B cell malignancy includes, but is not limited to, leukemia and non-Hodgkin's lymphoma (column 2, lines 48-54 and column 6, lines 16-21). With regards to the patient, the patent teaches that the patients include, but are not limited to, humans (column 6, lines 56-57). With regards to the administration, the patent teaches that the combination can be administered intravenously (column 12, lines 1-2).

Claims 113-121, 124-127, 131-134 and 142 are rejected under 35 U.S.C. 102(b) as being anticipated by Goldenberg (US 6,183,477, 2001).

Goldenberg teaches a method of treating a B cell malignancy in a patient comprising administering a therapeutically effective amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody component with a therapeutic agent (column 4, lines 25-26 and column 11, lines 5-8). For example, the patent teaches that anti-CD22 antibody immunoconjugates can be used to treat both indolent and aggressive forms of Non-

Hodgkin's lymphoma (column 11, lines 11-14). In addition to Non-Hodgkin's lymphoma, the patent teaches that the immunoconjugates are useful for the treatment of chronic lymphatic leukemias, and acute lymphatic leukemias (column 11, lines 8-11). Regarding the therapeutic agent of the immunoconjugate, the patent teaches that useful therapeutic agents for the preparation of the immunoconjugate include, but are not limited to, cancer chemotherapeutic drugs such as nitrogen mustards, alkyl sulfonates, nitrosoureas, triazenes and folic acid analogs (column 12, lines 61+). With regards to the administration, the patent teaches that the immunoconjugates can be administered intravenously (column 14, lines 8-15). The patent further teaches that the immunoconjugate can be administered in combination with another biological agent or chemotherapeutic regimen such as in combination with an anti-CD19 or anti-CD20 antibodies or administered in combination with chemotherapeutic regimes for treatment of intermediate grade non-Hodgkin's lymphoma including, but not limited to, C-MOPP, CHOP or M-BACOD (column 13, lines 29-63).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 128-130 and 143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldenberg (US 6,183,477, 2001) in view of Trail et al. (Current Opinion in Immunology 1999, 11: 584-588).

Goldenberg teaches, as applied to claims 113-121, 124-127, 131-134 and 142 above, a method of treating a B cell malignancy in a patient comprising administering a therapeutically effective amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody component with a therapeutic agent (column 4, lines 25-26 and column 11, lines 5-8). For example, the patent teaches that anti-CD22 antibody immunoconjugates can be used to treat both indolent and aggressive forms of Non-Hodgkin's lymphoma (column 11, lines 11-14).

In addition to Non-Hodgkin's lymphoma, the patent teaches that the immunoconjugates are useful for the treatment of chronic lymphatic leukemia's, and acute lymphatic leukemia's (column 11, lines 8-11). Regarding the therapeutic agent of the immunoconjugate, the patent teaches that useful therapeutic agents for the preparation of the immunoconjugate include, but are not limited to, cancer chemotherapeutic drugs such as nitrogen mustards, alkyl sulfonates, nitrosoureas, triazenes, folic acid analogs pyrimidine analogs, purine analogs, antibiotics, epipodophyllotoxins, platinum coordination complexes and hormones (column 12, lines 61+). With regards to the administration, the patent teaches that the immunoconjugates can be administered intravenously (column 14, lines 8-15). The patent further teaches that the immunoconjugate can be administered in combination with another biological agent or chemotherapeutic regimen such as in combination with an anti-CD19 or anti-CD20 antibodies or administered in combination with chemotherapeutic regimes for treatment of intermediate grade non-Hodgkin's lymphoma including, but not limited to, C-MOPP, CHOP or M-BACOD (column 13, lines 29-63).

Goldenberg does not explicitly teach that the therapeutic agent portion of the conjugate is the antibiotic, calicheamicin.

Trail et al. teach monoclonal antibody drug conjugates in the treatment of cancer. Specifically, the reference teaches that members of the enediyne family of antibiotics such as calicheamicin are among the most toxic antitumor compounds described to date, but there utility as antitumor dugs has-for the most part-been limited by their low therapeutic index (page 584, 2nd column, last sentence to page 585, 1st column). Trail et al. further teach that anti-body directed delivery provides a potential means to exploit the impressive potency of these compounds while minimizing their systemic toxicity (page 585, 1st column, 1st paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use calicheamicin, a species of antibiotics, in the method taught by Goldenberg in view of Trail et al. teachings that calicheamicin are among the most toxic antitumor antibiotics described to date. One would have been motivated to do so because Trail et al. teaches that antibody-directed delivery of calicheamicin provides a potential means to exploit this impressive potency while minimizing their systemic toxicity. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering a conjugate comprising calicheamicin and an anti-CD22 antibody, one would achieve an effective method of treating a B-cell malignancy.

Claim 134 is rejected under 35 U.S.C. 103(a) as being unpatentable over Goldenberg (US 6,183,477, 2001) in view of Maloney et al. (Blood 1997; 90: 2188-2195).

Goldenberg teaches, as applied to claims 113-121, 124-127, 131-134 and 142 above, a method of treating a B cell malignancy in a patient comprising administering a therapeutically effective amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody component with a therapeutic agent (column 4, lines 25-26 and column 11, lines 5-8). For example, the patent teaches that anti-CD22 antibody immunoconjugates can be used to treat both indolent and aggressive forms of Non-Hodgkin's lymphoma (column 11, lines 11-14). In addition to Non-Hodgkin's lymphoma, the patent teaches that the immunoconjugates are useful for the treatment of chronic lymphatic leukemia's, and acute lymphatic leukemia's (column 11, lines 8-11). Regarding the therapeutic agent of the immunoconjugate, the patent teaches that useful therapeutic agents for the preparation of the immunoconjugate include, but are not limited to, cancer chemotherapeutic drugs such as nitrogen mustards, alkyl sulfonates, nitrosoureas, triazenes, folic acid analogs pyrimidine analogs, purine analogs, antibiotics, epipodophyllotoxins, platinum coordination complexes and hormones (column 12, lines 61+). With regards to the administration, the patent teaches that the immunoconjugates can be administered intravenously (column 14, lines 8-15). The patent further teaches that the immunoconjugate can be administered in combination with another biological agent or chemotherapeutic regimen such as in combination with an anti-CD19 or anti-CD20 antibodies or administered in combination with chemotherapeutic regimes for treatment of intermediate grade non-Hodgkin's lymphoma including, but not limited to, C-MOPP, CHOP or M-BACOD (column 13, lines 29-63).

Goldenberg does not explicitly teach that the immunoconjugate is administered in combination with Rituximab, an anti-CD19 antibody.

Maloney et al. teach a method of treating low-grade Non-Hodgkin's lymphoma, comprising administering to a patient in need thereof a therapeutically effective amount of Rituximab (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of treating Non-Hodgkin's lymphoma comprising administering an immunoconjugate comprising an anti-CD22 antibody as taught by Goldenbert with Rixuximab in view of Maloney et al' teachings that Rituximab is effective at treating Non-Hodgkin's

lymphoma because each of the agents have been individually taught in the prior art for the treatment of lymphoma. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, one of ordinary skill in the art would have a reasonable expectation of success that by administering a immunoconjugate comprising an anti-CD22 antibody in combination with Rituximab, one would achieve an effective method of treating a B-cell malignancy.

Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 113 and 116 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 48 of copending Application No. 11/221,902.

Although the conflicting claims are not identical, they are not patentably distinct from each other because a species anticipates a genus. The species method of treating a subject having a 5T4-positive cancer, comprising administering to the subject a therapeutically effective amount of an anti-5T4 antibody/drug conjugate comprising (i) a chimeric or humanized anti-5T4 antibody and (ii) a therapeutic agent bound to the antibody claimed in the conflicting application appears to fall within the same scope of the genus method of treating a subject with a proliferative disorder, the method comprising administering a therapeutically effective dose of a composition comprising a cytotoxic derivative/carrier conjugate claimed in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 113 and 116 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 88 and 99 of copending Application No. 11/080,587.

Although the conflicting claims are not identical, they are not patentably distinct from each other because a species anticipates a genus. The species method of treating cancer comprising administering a therapeutically effective amount of a composition comprising a conjugate of a calicheamicin covalently linked to an anti-Lewis Y antibody claimed in the conflicting application appears to fall within the same scope of the genus method of treating a subject with a proliferative disorder, the method comprising administering a therapeutically effective dose of a composition comprising a cytotoxic derivative/carrier conjugate claimed in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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